Six1 transcription factor is critical for coordination of epithelial, mesenchymal and vascular morphogenesis in the mammalian lung.

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Public Summary:

Scientific Abstract:
Six1 is a member of the six-homeodomain family of transcription factors. Six1 is expressed in multiple embryonic cell types and plays important roles in proliferation, differentiation and survival of precursor cells of different organs, yet its function during lung development was hitherto unknown. Herein we show that Six1(-/-) lungs are severely hypoplastic with greatly reduced epithelial branching and increased mesenchymal cellularity. Six1 is expressed at the distal epithelial tips of branching tubules as well as in the surrounding distal mesenchyme. Six1(-/-) lung epithelial cells show increased expression of differentiation markers, but loss of progenitor cell markers. Six1 overexpression in MLE15 lung epithelial cells in vitro inhibited cell differentiation, but increases the expression of progenitor cell markers. In addition, Six1(-/-) embryos and newborn mice exhibit mesenchymal overproliferation, decreased Fgf10 expression and severe defects in the smooth muscle component of the bronchi and major pulmonary vessels. These defects lead to rupture of major vessels in mutant lungs after birth. Treatment of Six1(-/-) epithelial explants in culture with recombinant Fgf10 protein restores epithelial branching. As Shh expression is abnormally increased in Six1(-/-) lungs, we also treated mutant mesenchymal explants with recombinant Shh protein and found that these explants were competent to respond to Shh and continued to grow in culture. Furthermore, inhibition of Shh signaling with cyclopamine stimulated Six1(-/-) lungs to grow and branch in culture. This study provides the first evidence for the requirement of Six1 in coordinating Shh-Fgf10 signaling in embryonic lung to ensure proper levels of proliferation and differentiation along the proximodistal axis of epithelial, mesenchymal and endothelial cells. These findings uncover novel and essential functions for Six1 as a critical coordinator of Shh-Fgf10 signaling during embryonic lung development. We propose that Six1 is hence critical for coordination of proper lung epithelial, mesenchymal and vascular development.